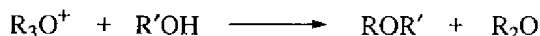


Exhibit B

Sections 10-21, 16-6, 16-7, 16-8, and 16-56 from
Smith, M.B., and March, J. March's Advanced Organic Chemistry,
5th ed., Wiley (New York, N.Y., 2001)

10-19 Alkylation With Onium Salts

ALKOXY-DE-HYDROXYLATION

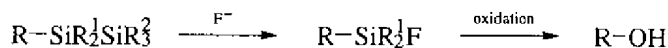
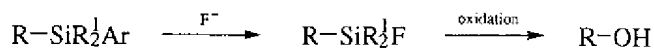


Oxonium ions are excellent alkylating agents, and ethers can be conveniently prepared by treating them with alcohols or phenols.⁶⁹⁶ Quaternary ammonium salts can sometimes also be used.⁶⁹⁷

OS VIII, 536.

10-20 Hydroxylation of Silanes

HYDROXY-DE-SILYLALKYLATION

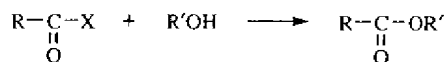


Alkylsilanes can be oxidized, with the silyl unit converted to a hydroxy unit. This requires either an aryl group⁶⁹⁸ or another silyl group⁶⁹⁹ attached to silicon. Treatment with a fluorinating agent such as tetrabutylammonium fluoride or CsF replaces Ar or SiR₃ with F, which is oxidized with hydrogen peroxide or a peroxy acid to give the alcohol. This sequence is often called the *Tamao-Fleming oxidation*.⁶⁹⁸ There are several variations in substrate that allow versatility in the initial incorporation of the silyl unit.⁷⁰⁰

D. Attack by OR at an Acyl Carbon

10-21 Alcoholysis of Acyl Halides

ALKOXY-DE-HALOGENATION



The reaction between acyl halides and alcohols or phenols is the best general method for the preparation of carboxylic esters. It is believed to proceed by a S_N2 mechanism.⁷⁰¹ As with 10-8, the mechanism can be S_N1 or tetrahedral.⁵⁵⁹ Pyridine catalyzes the reaction by the nucleophilic catalysis route (see 10-9). The reaction is of wide scope, and many functional groups do not interfere. A base is frequently added to combine with the HX formed. When aqueous alkali is used, this is called the *Schotten-Baumann procedure*, but pyridine is also frequently used. Both R and R' may be primary, secondary, or tertiary alkyl or aryl. Enolic esters can also be prepared by this method, though C-acylation competes in these cases. In difficult cases, especially with hindered acids or tertiary R', the alkoxide can be used instead of the alcohol.⁷⁰² Activated alumina has also been used as a catalyst, for tertiary R'.⁷⁰³ Thallium salts of phenols give very high yields of phenolic esters.⁷⁰⁴ Phase-transfer catalysis has been used for hindered phenols.⁷⁰⁵ Zinc has been used to couple alcohols and acyl chlorides.⁷⁰⁶ Selective acylation is possible in some cases.⁷⁰⁷

When phosgene is obtained.

Cl-

An important example from phosgene and amino groups during

Acyl halides react with ester.⁷⁰⁸

Acyl halides can react with alcohols, in MeCN



This is a method:

OS I, 12; III, 1; V, 1, 166, 168, 17

10-22 Alcoholysis

ALKOXY-DE-ACYLATION



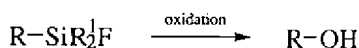
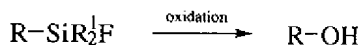
The scope of this reaction is somewhat less restricted than for esters. Acids, L, pyridine.⁷¹⁰ Catalysts (Dimethylamino) where pyridine TaCl₅-SiO₂.⁷¹³ acid can be prepared as anhydride. Cycl

Alcohols can be acetylated with acetic-phosphoric acid. OS I, 285, 833; IV, 15, 241, 258.

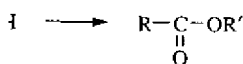
ION



g agents, and ethers can be conveniently prepared from alcohols or phenols.⁶⁹⁶ Quaternary ammonium salts

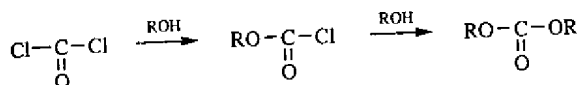


silyl unit converted to a hydroxy unit. The silyl group⁶⁹⁹ attached to silicon. Treatment with tributylammonium fluoride or CsF replaces the silyl group with a hydrogen peroxide or a peroxy acid to give the *Tamao-Fleming oxidation*.⁶⁹⁸ The reaction shows great versatility in the initial incorporation of



alcohols or phenols is the best general method. It is believed to proceed by a $\text{S}_{\text{N}}2$ mechanism, but it can be $\text{S}_{\text{N}}1$ or tetrahedral.⁵⁵⁹ Pyridine catalysis route (see 10-9). The reaction is of the $\text{S}_{\text{N}}2$ type and does not interfere. A base is frequently added. In an aqueous alkali is used, this is called the *Reimer-Tiemann reaction*. The same reaction is also frequently used. Both R and R' can be alkyl or aryl. Enolic esters can also be prepared. In difficult cases, the alkoxide can be used instead of the alcohol. It has been used as a catalyst, for tertiary R'.⁷⁰⁰ Yields of phenolic esters.⁷⁰⁴ Phase-transfer catalysis.⁷⁰⁵ Zinc has been used to couple alcohols and phenols.⁷⁰⁷ Acylation is possible in some cases.

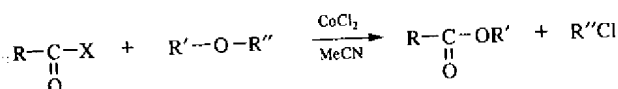
phosgene is the acyl halide, haloformic esters or carbonates can be prepared.



An important example is the preparation of carbobenzoxy chloride ($\text{PhCH}_2\text{OCOCl}$) from phosgene and benzyl alcohol. This compound is widely used for protection of amino groups during peptide synthesis (see 10-55).

Acyl halides react with thiols, in the presence of zinc, to give the corresponding thioester.⁷⁰⁸

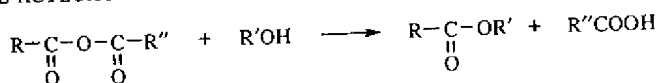
Acyl halides can also be converted to carboxylic acids by using ethers instead of alcohols, in MeCN in the presence of certain catalysts such as cobalt(II) chloride.⁷⁰⁹



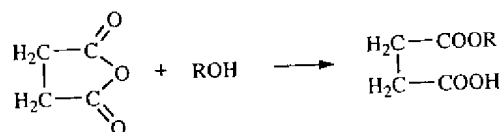
This is a method for the cleavage of ethers (see also 10-71).
OS I, 12; III, 142, 144, 167, 187, 623, 714; IV, 84, 263, 478, 479, 608, 616, 788; V, 1, 166, 168, 171; VI, 199, 259, 312, 824; VII, 190; VIII, 257, 516.

10-22 Alcoholysis of Anhydrides

ALKOXY-DE-ACYLOXY-SUBSTITUTION

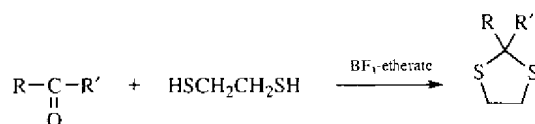


The scope of this reaction is similar to that of 10-21. Though anhydrides are somewhat less reactive than acyl halides, they are often used to prepare carboxylic esters. Acids, Lewis acids, and bases are often used as catalysts—most often, pyridine.⁷¹⁰ Catalysis by pyridine is of the nucleophilic type (see 10-9). 4-(*N,N*-Dimethylamino)pyridine is a better catalyst than pyridine and can be used in cases where pyridine fails.⁷¹¹ Nonbasic catalysts are cobalt(II) chloride⁷¹² and $\text{TiCl}_4\text{-SiO}_2$.⁷¹³ Formic anhydride is not a stable compound but esters of formic acid can be prepared by treating alcohols⁷¹⁴ or phenols⁷¹⁵ with acetic-formic anhydride. Cyclic anhydrides give monoesterified dicarboxylic acids, for example,



Alcohols can also be acylated by mixed organic-inorganic anhydrides, such as acetic-phosphoric anhydride, $\text{MeCOOPO}(\text{OH})_2$ (see 10-35).⁷¹⁶
OS I, 285, 418; II, 69, 124; III, 11, 127, 141, 169, 237, 281, 428, 432, 833; IV, 15, 242, 304; V, 8, 459, 591, 887; VI, 121, 245, 560, 692; 486; VII, 141, 258.

acetals, are stable in the presence of bases, except that a strong base can remove an aldehyde proton, if there is one (see **10-107**)⁸⁶. A common method for the protection of ketones involves treatment with ethanedithiol to give a cyclic dithioketal.⁸⁷ After subsequent reactions involving the R or R' group, the protecting group can be

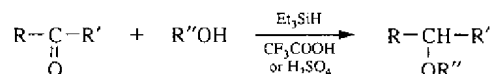


be removed by **10-6**. Alternatively, the dithioacetal can be desulfurized with Raney nickel (**14-34**), giving the overall conversion $C=O \rightarrow CH_2$. Dithioacetals can also be prepared from aldehydes or ketones by treatment with thiols in the presence of $TiCl_4$,⁸⁸ $SiCl_4$,⁸⁹ with a disulfide ($RSSR$; R = alkyl or aryl),⁹⁰ or with methyltrimethylsilane ($MeSSiMe_3$).⁹¹

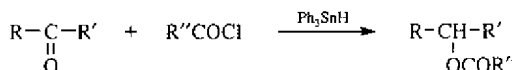
OS I, 1, 298, 364, 381; II, 137; III, 123, 387, 502, 536, 644, 731, 800; IV, 21, 479, 679; V, 5, 292, 303, 450, 539; VI, 567, 666, 954; VII, 59, 149, 168, 177, 241, 271, 297; VIII, 357. Also see OS IV, 558, 588; V, 25; VIII, 415.

16-6 Reductive Alkylation of Alcohols

C-HYDRO-O-ALKYL-ADDITION



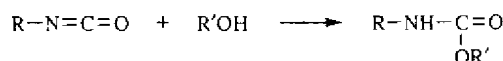
Aldehydes and ketones can be converted to ethers by treatment with an alcohol and triethylsilane in the presence of a strong acid⁹² or by hydrogenation in alcoholic acid in the presence of platinum oxide.⁹³ The process can formally be regarded as addition of ROH to give a hemiacetal $RR'C(OH)OR''$, followed by reduction of the OH. In this respect, it is similar to 16-14. In a similar reaction, ketones can be converted to carboxylic esters (reductive acylation of ketones) by treatment with an acyl chloride and triphenyltin hydride.⁹⁴



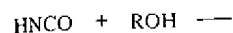
Ethers have also been prepared by the reductive dimerization of two molecules of an aldehyde or ketone (e.g., cyclohexanone \rightarrow dicyclohexyl ether). This was accomplished by treatment of the substrate with a trialkylsilane and a catalyst.⁹⁹

16-7 The Addition of Alcohols to Isocyanates

N-HYDRO-C-ALKOXY-ADDITION



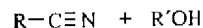
amates (substituted urethanes). This is an excellent
 organic acid HNCO gives unsaturated
 CO gives *allophanates*.



urethanes are made by compounds containing two OH groups (RNHCSOR'),⁹⁶ though the details of the mechanism of attack of alcohol is certainly attacking the carbonyl group. This complicates the kinetic picture analyzed by metallic compounds, such as sodium, potassium, or oxides¹⁰¹ or *n*-butyllithium (see Table I, 140; V, 162; VI, 95,

6-8 Alcoholysis of Nitrile

OXO,OXO-DE-NITRIL-TER



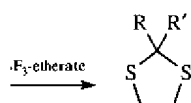
The addition of dry HCl to a solution of an imino ester in water leads to the hydrochloride (salts and imino ethers). The imino ester can be converted to the free amine, sodium bicarbonate, or it can be converted to the corresponding carboxylic ester. The imino ester can be converted to the corresponding carboxylic ester by heating, in which case aqueous acid is eliminated. Imino esters can be converted to the corresponding carboxylic ester by heating, in which case aqueous acid is eliminated. Imino esters can be converted to the corresponding carboxylic ester by heating, in which case aqueous acid is eliminated.

This reaction is of broad applicability for the synthesis of monosubstituted and with no diester. Cyanogen chloride reacts with HCl or AlCl_3 to give car



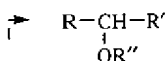
The alcohol ROH can also be used as a solvent. See QS I, 5, 270; II, 284, 310.

that a strong base can remove the common method for the protection to give a cyclic dithioketal.⁸⁷ After up, the protecting group can then

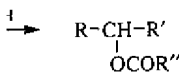


al can be desulfurized with Raney $\text{D} \rightarrow \text{CH}_2$. Dithioacetals can also be with thiols in the presence of kyl or aryl),⁹⁰ or with methylthio

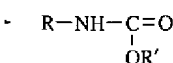
22, 536, 644, 731, 800; IV, 21, 479, VII, 59, 149, 168, 177, 241, 271; VIII, 415.



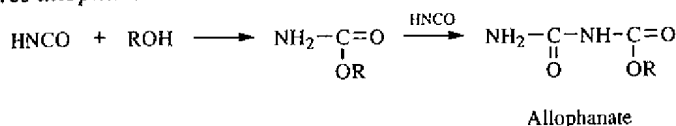
s by treatment with an alcohol and by hydrogenation in alcoholic acid. This can formally be regarded as OR'', followed by reduction of the similar reaction, ketones can be n of ketones) by treatment with an



e dimerization of two molecules of dicyclohexyl ether). This was ac trialkylsilane and a catalyst.⁹⁵



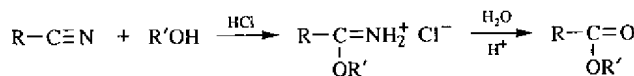
amates (substituted urethanes) are prepared when isocyanates are treated with alcohols. This is an excellent reaction, of wide scope, and gives good yields. Cyanic acid HNCO gives unsubstituted carbamates. Addition of a second mole of HNCO gives allophanates.



urethanes are made by combining compounds with two NCO groups with compounds containing two OH groups. Isothiocyanates similarly give thiocarbamates ($\text{RNHCSOR}'$),⁹⁶ though they react slower than the corresponding isocyanates. The details of the mechanism are poorly understood,⁹⁷ though the oxygen of the alcohol is certainly attacking the carbon of the isocyanate. Hydrogen bonding complicates the kinetic picture.⁹⁸ The addition of ROH to isocyanates can also be catalyzed by metallic compounds,⁹⁹ by light,¹⁰⁰ or, for tertiary ROH, by lithium oxides¹⁰¹ or *n*-butyllithium.¹⁰² OS I, 140; V, 162; VI, 95, 226, 788, 795.

16-8. Alcoholysis of Nitriles

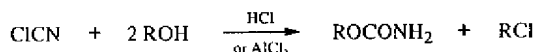
ALKOXY,OXO-DE-NITRILLO-TERSUBSTITUTION



The addition of dry HCl to a mixture of a nitrile and an alcohol in the absence of water leads to the hydrochloride salt of an imino ester (imino esters are also called imidates and imino ethers). This reaction is called the *Pinner synthesis*.¹⁰³ The salt can be converted to the free imino ester by treatment with a weak base such as sodium bicarbonate, or it can be hydrolyzed with water and an acid catalyst to the corresponding carboxylic ester. If the latter is desired, water may be present from the beginning, in which case aqueous HCl can be used and the need for gaseous HCl is eliminated. Imino esters can also be prepared from nitriles with basic catalysts.¹⁰⁴

This reaction is of broad scope and is good for aliphatic, aromatic, and heterocyclic R and for nitriles with oxygen-containing functional groups. The application of the reaction to nitriles containing a carboxyl group constitutes a good method for the synthesis of mono esters of dicarboxylic acids with the desired group identified and with no diester or diacid present.

Cyanogen chloride reacts with alcohols in the presence of an acid catalyst such as dry HCl or AlCl_3 to give carbamates.¹⁰⁵



The alcohol ROH can also be added to nitriles in another manner (16-56). OS I, 5, 270; II, 284, 310; IV, 645; VI, 507; VIII, 415.

by using the benzoylated cyanohydrin as one of the components in a phase-transfer catalyzed process. By this means products can be obtained from aldehydes that normally fail to self-condense.⁸⁶⁰

OS I, 94; VII, 95.

16-55 Addition of Radicals to C=O, C=S, C=N Compounds

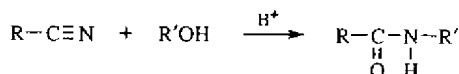
Radical cyclization is not limited to a radical attacking a C=C unit (see 15-35 and 15-36), and reactions with both C=N and C=O moieties are known. Reaction of $\text{MeON}=\text{CH}(\text{CH}_2)_3\text{CHO}$ with Bu_3SnH and AIBN, for example led to *trans*-2-(methoxyamino)cyclopentanol in good yield.⁸⁶¹ Addition of radical to the C=N unit of $\text{R}-\text{C}=\text{N}-\text{SPh}$ ⁸⁶² or $\text{R}-\text{C}=\text{N}-\text{OBz}$ ⁸⁶³ led to cyclic imines. Radical addition to simple imines leads to aminocycloalkenes.⁸⁶⁴ Radical also add to the carbonyl unit of phenylthio esters to give cyclic ketones.⁸⁶⁵

Reactions in Which Carbon Adds to the Hetero Atom

A. Oxygen Adding to the Carbon

16-56 The Ritter Reaction

N-HYDRO,N-ALKYL-C-OXO-BIADDITION



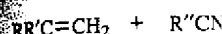
Alcohols can be added to nitriles in an entirely different manner from that of Reaction 16-8. In this reaction, the alcohol is converted by a strong acid to a carbocation, which adds to the negative nitrogen, water adding to the carbon:



The immediate product tautomerizes to the N-alkyl amide. Only alcohols that give rise to fairly stable carbocations react (secondary, tertiary, benzylic, etc.); primary alcohols do not give the reaction. The carbocation need not be generated from an alcohol but may come from protonation of an alkene or from other sources. In any case, the reaction is called the *Ritter reaction*.⁸⁶⁶ Hydrogen cyanide also gives the reaction, the product being a formamide. Trimethylsilyl cyanide has also been used.⁸⁶⁷ Since the amides (especially the formamides) are easily hydrolyzable to amines, the Ritter reaction provides a method for achieving the conversions $\text{R}'\text{OH} \rightarrow \text{R}'\text{NH}_2$ (see 10-46) and $\text{alkene} \rightarrow \text{R}'\text{NH}_2$ (see 15-8) in those cases where R' can form a relatively stable carbocation. The reaction is especially useful for the preparation of tertiary alkyl amines because there are few alternate ways of preparing these compounds. The reaction can be extended to primary alcohols by

reacting with triflic acid in the presence of the nitrile.

Alkenes of the form $\text{R}-\text{CH}=\text{CH}_2$ react with mercuric nitrate to give products obtained by the Ritter reaction with strong acids.



The Ritter reaction of $\text{R}-\text{CH}=\text{CH}_2$ with $\text{R}'\text{NHCONHR}'$ (see 16-57) is also known.⁸⁷¹ OS V, 73, 471.

16-57 Acylation of Alkenes

ACYL-C-ACYLOXY-ADDITION

$\text{R}-\text{CH}=\text{CH}_2 + \text{R}'\text{COCl} \xrightarrow{\text{R}''\text{O}^-} \text{R}-\text{CH}(\text{R}')-\text{CH}_2-\text{OR}''$

Aldehydes can be converted to ketones in the presence of BF_3 , other reagents. This reaction cannot normally be applied to aldehydes because the reagent is trichloroaluminum.⁸⁷⁵

OS IV, 489.

16-58 The Addition of Alcohols to Aldehydes

When catalyzed by acids, aldehydes form cyclic acetals, the most common of which is formaldehyde. This is called *paraformaldehyde*. Under certain conditions, aldehydes can also polymerize. This is required to form hemiacetals. Hemiacetals are formed from formaldehyde and aldehydes are acetals. Because formaldehyde is so convenient to use them

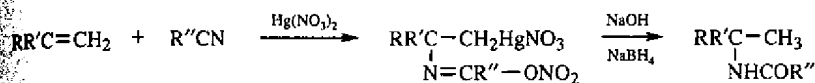
omponents in a phase-transfer
obtained from aldehydes that

=N Compounds

ing a C=C unit (see 15-35 and
eties are known. Reaction of
for example led to *trans*-2-
ion of radical to the C=N unit
lic imines. Radical addition to
also add to the carbonyl unit

treatment with triflic anhydride⁸⁶⁸ or $\text{Ph}_2\text{CCl}^+ \text{SbCl}_6^-$ or a similar salt⁸⁶⁹ in the
presence of the nitrile.

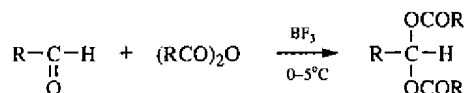
Alkenes of the form $\text{RCH}=\text{CHR}'$ and $\text{RR}'\text{C}=\text{CH}_2$ add to nitriles in the presence
of mercuric nitrate to give, after treatment with NaBH_4 , the same amides that would
be obtained by the Ritter reaction.⁸⁷⁰ This method has the advantage of avoiding
strong acids.



The Ritter reaction can be applied to cyanamides RNHCN to give ureas
($\text{RNHCONHR}'$).⁸⁷¹
OS V, 73, 471.

16-57 Acylation of Aldehydes and Ketones

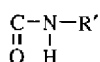
16-57 ACYL-C-ACYLOXY-ADDITION



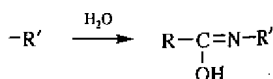
Aldehydes can be converted to *acylals* by treatment with an anhydride in the
presence of BF_3 , other Lewis acids,⁸⁷² proton acids,⁸⁷³ or PCl_3 .⁸⁷⁴ The reaction
cannot normally be applied to ketones, though an exception has been reported when
the reagent is trichloroacetic anhydride, which gives acylals with ketones without a
catalyst.⁸⁷⁵

OS IV, 489.

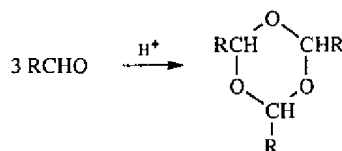
16-58 The Addition of Aldehydes to Aldehydes



fferent manner from that of
verted by a strong acid to a
er adding to the carbon:



nide. Only alcohols that give
ary, benzylic, etc.); primary
ed not be generated from an
or from other sources. In any
rogen cyanide also gives the
silyl cyanide has also been
s) are easily hydrolyzable to
achieving the conversions
e 15-8) in those cases where
on is especially useful for the
are few alternate ways of
ended to primary alcohols by



When catalyzed by acids, low molecular weight aldehydes add to each other to give
cyclic acetals, the most common product being the trimer.⁸⁷⁶ The cyclic trimer of
formaldehyde is called *trioxane*,⁸⁷⁷ and that of acetaldehyde is known as
paraformaldehyde. Under certain conditions, it is possible to get tetramers⁸⁷⁸ or dimers.
Aldehydes can also polymerize to linear polymers, but here a small amount of water
is required to form hemiacetal groups at the ends of the chains. The linear polymer
formed from formaldehyde is called *paraformaldehyde*. Since trimers and polymers
of aldehydes are acetals, they are stable to bases but can be hydrolyzed by acids.
Because formaldehyde and acetaldehyde have low boiling points, it is often
convenient to use them in the form of their trimers or polymers.